

CLAIMS.

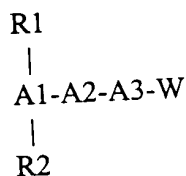
Various features of the invention are emphasized in the claims which follow.

What is claimed is:

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1. A compound having the formula:



wherein:

each R1 and R2, independently, is H, C1-C12 alkyl (*e.g.*, methyl), C6-C18 aryl (*e.g.*, phenyl), C1-C18 acyl (*e.g.*, formyl, acetyl, and myristoyl), C7-C18 aralkyl (*e.g.*, benzyl), C7-C18 alkaryl (*e.g.*, p-methylphenyl) or a dihydrotrigonellinate group;

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A1 is a D or L-amino acid selected from the group consisting of Cys, Leu, Dap, Trp, Gln, a tethered amino acid with an indole ring (*e.g.*, N-Me-Trp), Phe, Hyp, any Trp derivative (*e.g.*, 2 chlorotryptophan, or Tcc); CaMe-Trp, CaMe-Gln, Des-amino-Trp, Pyr, Bth, Nal, Tcc, Asn, Nva, Abu, Tyr, Tic-OH, Phe, Tip, and Dip;

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A2 is a D or L-amino acid selected from the group consisting of Cys, Trp, Arg, N-Me-Arg, CaMe-Arg, Orn, Cit, hArg(R)₂ [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl], Lys-ε-NH-R [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl];

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A3 is a D or L-amino acid selected from the group consisting of Glu, N-Me-Tyr, CaMe-Tyr, Tic-OH, Tic, Dip, Trp, Phe, des-carboxylic-Tyr (tyramine), and Tyr-(R) [where R is hydrogen or a lipophilic group, *e.g.*, myristoyl, cholesteryl, t.Bu, *etc.*];

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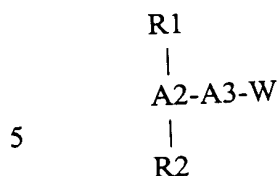
W is -OH, -N-R₃R₄, or OR₅ (where R₃, R₄, and R₅, independently, is H, C1-C12 alkyl (e.g., methyl), C6-C18 aryl (e.g., phenyl), C1-C12 acyl (e.g., formyl, acetyl, and myristoyl), C7-C18 aralkyl (e.g., benzyl), or C7-C18 alkaryl (e.g., p-methylphenyl); or a pharmaceutically acceptable salt thereof;

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and
each bond between two amino acids or amino acid derivatives, represented by a dash ("-"), can be either a peptide bond or a pseudopeptide bond or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein said compound has a formula selected from the group consisting of N- α -Ac-Trp-Arg-Tyr-NH₂, Ac-Gln-Arg-Tyr-NH₂, Ac-Tcc-Arg-Tyr-NH₂, Ac-Trp-Arg-Tic(OH)-NH₂, and Ac-Tcc-Arg-Tic(OH)-NH₂.

3. A compound having the formula:



wherein:

10 each R1 and R2, independently, is H, C1-C12 alkyl (*e.g.*, methyl), C6-C18 aryl (*e.g.*, phenyl), C1-C18 acyl (*e.g.*, formyl, acetyl, and myristoyl), C7-C18 aralkyl (*e.g.*, benzyl), C7-C18 alkaryl (*e.g.*, p-methylphenyl) or a dihydrotrigonellinate group;

15 A2 is a D or L-amino acid selected from the group consisting of Cys, Trp, Arg, N-Me-Arg, CaMe-Arg, Orn, Cit, hArg(R)₂ [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl], Lys-ε-NH-R [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl];

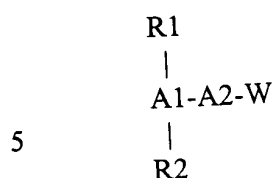
20 A3 is a D or L-amino acid selected from the group consisting of Glu, N-Me-Tyr, CaMe-Tyr, Tic-OH, Tic, Dip, Trp, Phe, des-carboxylic-Tyr (tyramine), and Tyr-(R) [where R is hydrogen or a lipophilic group, *e.g.*, myristoyl, cholesteryl, t.Bu, *etc.*];

25 W is -OH, -N-R₃R₄, or OR₅ (where R₃, R₄, and R₅, independently, is H, C1-C12 alkyl (*e.g.*, methyl), C6-C18 aryl (*e.g.*, phenyl), C1-C12 acyl (*e.g.*, formyl, acetyl, and myristoyl), C7-C18 aralkyl (*e.g.*, benzyl), or C7-C18 alkaryl (*e.g.*, p-methylphenyl); or a pharmaceutically acceptable salt thereof; and

each bond between two amino acids or amino acid derivatives, represented by a dash ("-"), can be either a peptide bond or a pseudopeptide bond or a pharmaceutically acceptable salt thereof.

continued

4. A compound having the formula:



wherein:

10 each R1 and R2, independently, is H, C1-C12 alkyl (*e.g.*, methyl), C6-C18 aryl (*e.g.*, phenyl), C1-C18 acyl (*e.g.*, formyl, acetyl, and myristoyl), C7-C18 aralkyl (*e.g.*, benzyl), C7-C18 alkaryl (*e.g.*, p-methylphenyl) or a dihydrotrigonellinate group;

15 A1 is a D or L-amino acid selected from the group consisting of Cys, Leu, Dap, Trp, Gln, a tethered amino acid with an indole ring (*e.g.*, N-Me-Trp), Phe, Hyp, any Trp derivative (*e.g.*, 2 chlorotryptophan, or Tcc); CaMe-Trp, CaMe-Gln, Des-amino-Trp, Pyr, Bth, Nal, Tcc, Asn, Nva, Abu, Tyr, Tic-OH, Phe, Tip, and Dip;

20 A2 is a D or L-amino acid selected from the group consisting of Cys, Trp, Arg, N-Me-Arg, CaMe-Arg, Orn, Cit, hArg(R)2 [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl], Lys-ε-NH-R [where R is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, or alkylaryl];

25 W is -OH, -N-R3R4, or OR5 (where R3, R4, and R5, independently, is H, C1-C12 alkyl (*e.g.*, methyl), C6-C18 aryl (*e.g.*, phenyl), C1-C12 acyl (*e.g.*, formyl, acetyl, and myristoyl), C7-C18 aralkyl (*e.g.*, benzyl), or C7-C18

alkaryl (e.g., p-methylphenyl); or a pharmaceutically acceptable salt thereof;

and

each bond between two amino acids or amino acid derivatives, represented by a

dash ("-"), can be either a peptide bond or a pseudopeptide bond or a

5 pharmaceutically acceptable salt thereof.

5. The compound of claim 3, wherein said compound has the formula Ac-Arg-Tyr-NH₂.

6. The compound of claim 4, wherein said compound has the formula Ac-Trp-Arg-NH₂.

7. A compound according to claim 1 further having a formula selected from the group consisting of Cyclo-[-A1-A2-], Cyclo-[-A1-A2-A3-], Cyclo-[-A1-A2-A3-A1-A2-A3-], and Cyclo-[-A1-A2-A3-A3-A2-A1-].

8. The compound of claim 7, wherein said compound is selected from the group consisting of Cyclo (30/34)[Leu 30, Trp 32, Glu 34,]NPY (30-36)-NH₂, Cyclo (30/34)[Dap 30, Trp 32, Glu 34,]NPY (30-36)-NH₂, and N- α -Ac-Cyclo(29/34)[D-Cys 29,34, Trp32]NPY(29-36)-NH₂.

9. A compound according to claim 1 further having the formula:

Ac-[A1-A2-A3]_n-NH₂, wherein n = 1, 2, or 3.

10. The compound of claim 9, wherein, said compound is a dimer of the compounds of claim 1
11. The compound of claim 10, wherein said dimer is prepared by dimerizing the compound with dicarboxylic acids (*e.g.*, succinic acid), cystine, or diaminodicarboxylic acid (*e.g.*, 2,6-diaminopimelic acid).
12. The compound of claim 1, wherein said compound is conjugated to a carrier selected from the group consisting of cationized albumin and polylysine.
13. The compound of claim 1, wherein the said bond between two amino acids or amino acid derivatives is selected from the group consisting of C(O)NH, CH₂NH, CH₂-S, CH₂-O, CH₂-CH₂, CH₂-CO, and CH₂CH₂.
14. The compound of claim 13, wherein a pseudopeptide bond is positioned between A1 and A2.
15. The compound of claim 14, wherein a pseudopeptide bond is positioned between A2 and A3.

16. The compound of claim 3, wherein the said bond between two amino acids or amino acid derivatives is selected from the group consisting of C(O)NH, CH₂NH, CH₂-S, CH₂-O, CH₂-CH₂, CH₂-CO, and CH₂ CH₂).
17. The compound of claim 4, wherein the said bond between two amino acids or amino acid derivatives is selected from the group consisting of C(O)NH, CH₂NH, CH₂-S, CH₂-O, CH₂-CH₂, CH₂-CO, and CH₂ CH₂).
18. A therapeutic composition capable of controlling an NPY mediated physiological response comprising a therapeutically effective amount of the compound of claim 1, claim 3, claim 4, claim 7 or claim 9 together with a pharmaceutically acceptable carrier substance.
19. The composition of claim 18, wherein said composition is in the form of a pill, tablet, or capsule for oral administration to a subject in need of said compound.
20. The composition of claim 18, wherein said composition is in the form of a liquid for oral administration to a subject in need of said compound.
21. The composition of claim 18, wherein said composition being is in the form of a liquid for nasal administration as drops or spray to a subject in need of said composition.

22. The composition of claim 18, wherein said composition is in the form of a liquid for intravenous, subcutaneous, parenteral, or intraperitoneal administration to a subject in need of said composition.

23. The composition of claim 18, wherein said composition is in the form of a biodegradable sustained-release composition for intramuscular administration to a subject in need of said composition.

24. The composition of claim 18, wherein said composition includes a lipophilic salt and is suitable for administration in the form of an oil emulsion or dispersion to a subject in need of said composition.

25. A method for suppressing an NPY mediated physiological response in a subject comprising administering to said subject a compound of claim 1, claim 3, claim 4, claim 7 or claim 9.

26. The method of claim 25, wherein said administration lowers the blood pressure of said subject.

27. The method of claim 25, wherein said administration suppresses the appetite of said subject.

28. The method of claim 25, wherein said administration augments the libido of said subject.

29. The method of claim 25, wherein said administration stimulates cardiovascular function of said subject.

30. The method of claim 25, wherein said administration modulates the circadian rhythm of said subject.

31. A method of suppressing an NPY mediated physiological response in a tissue other than the heart in a subject comprising administering to said subject a compound of claim 1, claim 3, claim 4, claim 7 or claim 9.

32. The method of claim 31, wherein said compound suppresses the activity of the NPY receptor.

33. The method of claim 32, wherein said compound suppresses the activity of the NPY receptor.

34. A method of suppressing a NPY receptor mediated physiological response in the hypothalamus of a subject comprising administering to said subject the compound of claim 1.

35. A method of suppressing the blood pressure of a subject experiencing hypertension which comprises administering to said subject the compound of claim 1.

36. A method of suppressing a NPY receptor mediated physiological response in the cardiovascular system of a subject comprising administering to said subject the compound of claim 1.

37. A method for stimulating an NPY mediated physiological response in a subject comprising administering to said subject a compound of claim 1, claim 3, claim 4, claim 7 or claim 9.

38. The method of claim 37, wherein said administration increases the blood pressure of said subject.

39. The method of claim 38, wherein said administration increases the appetite of said subject.

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